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Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol

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Abstract

Introduction

Varicella zoster virus (VZV) causes varicella (chicken pox) and herpes zoster (shingles). Worldwide, these diseases are associated with significant morbidity. Most of the epidemiological data on VZV comes from high-income countries. There is little data on VZV in Africa, where tropical climates and high HIV/AIDS prevalence rates are expected to impact the epidemiology of VZV.

Safe and effective vaccinations for both varicella and herpes zoster exist, but are not routinely used in Africa. There is very little data available on VZV disease burden in Africa that could guide the introduction of these vaccines on the continent. Our aim is to conduct a systematic review of the VZV-associated morbidity and mortality in Africa, which will provide critical information that could be used to develop vaccination policies against these diseases in Africa.

Methods and Analysis

Electronic databases will be searched and all studies published after 1974 that meet predefined criteria will be assessed. The primary outcomes for the study are VZV incidence/prevalence, hospitalization rates and total death rates. The secondary outcome for this study is the proportion of VZV hospitalizations and/or deaths associated with HIV/AIDS.

Two reviewers will screen the titles and abstracts, and then independently review the full texts to determine if studies are eligible for inclusion. A risk of bias and quality assessment tool will be used to score all included studies. Following standardised data extraction, a trend analysis using R-programming software will be done to

investigate the trend of VZV. Depending on the characteristics of included studies, sub-group analyses will be performed. This review will be reported according to the PRISMA guidelines.

Ethics and Dissemination

As this is a protocol for a systematic review, which will use already published data, no ethics approval is required. Findings will be disseminated in peer-reviewed journals.

Systematic review registration: PROSPERO CRD42015026144 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026144)

Background

Varicella Zoster Virus (VZV), belonging to the Herpesviridae family, causes varicella (chicken pox) and later, through endogenous reactivation, herpes zoster (shingles). Both diseases occur worldwide, and while their mortality is generally low, these diseases have a high morbidity and place a large burden on healthcare systems and society (1). There is no synthesized literature on the burden of varicella and herpes zoster in Africa.

Varicella is characterised by a vesicular rash and fever, and in children is usually a mild, self-limiting illness. Complications, however, do occur, particularly in infants, pregnant women, adults and immunocompromised individuals, including those with HIV (1,2). Globally, there are 4,2 million cases of severe varicella that result in hospitalization or death each year (2). In temperate high income countries, 13-16 cases of varicella per 1000 population occur annually, with mostly children aged 1-9 years affected (1). In these settings more than 90% of the population becomes infected with VZV before adolescence (2). In tropical regions, primary infection of varicella tends to occur at a later stage, resulting in a larger population of susceptible adults and potentially a higher proportion of severe cases (2,3).

After an episode of varicella, VZV remains dormant in the dorsal root ganglia, and reactivation results in zoster, a painful vesicular rash, usually confined to one dermatome (4). The incidence of herpes zoster increases with increasing age, especially after 50 years of life. For example, amongst 85 year olds, half have experienced an episode of varicella (2). Decreasing cell mediated immunity due to, for example, HIV infection, cancer, diabetes mellitus and immunosuppressive

treatment also increase the risk of zoster (2). Compared to HIV negative individuals, persons with HIV have 12-17 fold greater risk of developing zoster. In areas with a high HIV prevalence, zoster has an 85-95% positive predictive value for underlying HIV infection (5). The most common complications of zoster are post-herpetic neuralgia and ocular complications (6). About 3% of zoster patients are hospitalized (7). There is little data on zoster mortality, but studies from Europe and North America suggest that it is around 0.25 per 1 million population, mostly in the elderly (7). Timely vaccination against zoster may prevent such deaths.

Effective vaccines exist for both varicella and zoster, and are used widely in high income countries, with considerable benefits (2). In 1998, WHO recommended the introduction of routine childhood vaccination against VZV in settings where the disease has significant negative socio-economic impact (8). But vaccines against VZV are rarely used on the African continent. Introducing these vaccines would be in agreement with the Global Immunization Vision and Strategy (GIVS) of the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF). The GIVS aims to widely introduce a range of newly available vaccines and immunize more people against as many vaccine-preventable diseases as possible (9). Achieving this aim would not only promote health, but also improve equitable access to immunization (9).

Decisions to introduce vaccines against varicella and zoster in most African countries need to be guided by evidence-based data on the epidemiology and socio-economic impacts of the diseases. To the best of our knowledge, at present, there is no synthesized VZV-associated epidemiological data in Africa. Furthermore, cost-

effectiveness studies of introducing the vaccines against varicella and shingles are lacking in Africa.

The African continent has several risk factors that could result in an increased burden of VZV disease. Firstly for varicella, there is a high prevalence of HIV/AIDS and, in tropical countries, primary infections occur at an older age, both of which increase the chance of developing severe varicella. Secondly for zoster, there is an increasing aging population, high HIV/AIDS burden and diabetes prevalence is growing (10,11). Thirdly, for both varicella and zoster, weak and overstretched healthcare systems in Africa cannot efficiently manage complications of these diseases.

Rationale

Globally, major variations in the epidemiology of VZV-associated disease exist. As such, some countries have adopted universal childhood vaccination against VZV while others recommend targeted vaccination of high risk populations only (1). In Africa, there is no collated evidence on the burden of varicella and zoster that could be used to inform decisions around vaccine introduction for these diseases. Furthermore, the impact of the HIV/AIDS pandemic on the epidemiology of VZV is also not clear, and any decisions around introduction of new vaccines on the continent would have to take this into account too.

Strengths and limitations of this study

The strengths of this study are:

- First time data on VZV in Africa collated

- Systematic review, reported according to PRISMA guidelines

The weaknesses of the study are:

- Only includes published studies, i.e. risk of publication bias
- May underestimate the burden of VZV in Africa

Methods

Objective

To describe the epidemiology of VZV in Africa, taking into account both clinical diseases of varicella and zoster.

Primary objectives

- To summarize the available data on the varicella-associated morbidity and mortality in Africa
- To summarize the available data on the herpes zoster-associated morbidity and mortality in Africa

Secondary objective

- To assess the impact of HIV/AIDS on the epidemiology of varicella and herpes zoster in Africa.

Eligibility criteria

Types of participants

Studies on the epidemiology of VZV, in adults and children, from any country in Africa, will be included in the review.

Case definition

Included studies must have clearly stated the case definition for varicella. The case definition for varicella, as defined by the Centres for Disease Control and Prevention (CDC), will be used for morbidity and mortality estimation (12):

Clinical description - An acute illness with diffuse maculo-papulovesicular rash, without other apparent cause.

Laboratory criteria - Isolation of varicella virus from a clinical specimen, OR Varicella antigen detected by direct fluorescent antibody test, OR Varicella-specific nucleic acid detected by polymerase chain reaction (PCR), OR Significant rise in serum anti-varicella immunoglobulin G (IgG) antibody level by any standard serologic assay.

The case definition of herpes zoster uses only the clinical description (painful maculo-papulovesicular rash, usually confined to a dermatome), as it has been shown to be distinctive enough to make an accurate clinical diagnosis (13).

Inclusion criteria

Studies will be included if they are conducted in Africa, measure or report any of the primary outcomes listed below and have a case definition for varicella or herpes zoster.

Exclusion criteria

Studies will be excluded from this review if they are not conducted in Africa, do not measure any of the primary outcomes listed below and have not stated a case definition of varicella or herpes zoster.

Outcomes

Primary outcomes

- Incidence or prevalence of varicella or herpes zoster

- Hospitalization rates associated with varicella or herpes zoster

-Total deaths associated with varicella or herpes zoster

Secondary outcomes

- Proportion of varicella or herpes zoster hospitalizations and/or deaths associated with HIV/AIDS

Type of studies

Case-series, cross-sectional, cohort and intervention studies will be included. All studies published from January 1974 to September 2015, will be included without language restrictions.

Search strategy

The literature search strategy will use both text words and medical subject heading (MeSH) terms and will include the following: varicella zoster virus, human herpes virus 3, varicella, chicken pox, herpes zoster or shingles, as well as prevalence, incidence, epidemiology, burden, hospitalisation or hospitalization, mortality or case-fatality rates. These terms will be adapted for each database and then be combined

with a relevant filter to select out studies from the African continent only. An example of the PubMed search strategy is shown in Table 1.

Electronic databases

The following electronic databases will be searched: PubMed, Scopus, Africa-wide, Embase, WHOLIS, PDQ-Evidence, CENTRAL, CINAHL and Web of Science.

Selection of eligible studies

The first and the second authors (HSH and LHA) will screen the search outputs using titles and abstracts. In addition, study setting, study design, methods as well as study outcomes will be evaluated. The two authors will then independently read through the full text of all potentially eligible studies to assess if inclusion criteria are met. Discrepancies in the list of included studies between the two authors will be resolved through discussion and consensus, with the assistance of the last author (BMK).

Data collection process

Data will be extracted from the included studies and recorded on a pre-designed form. If need be, corresponding authors for the included studies will be contacted where the relevant data is unclear. The following data will be extracted from the included studies:

- Study characteristics: year of the study publication, study design and objectives of the study
- Study population: country, community or healthcare facility based, and the source of the denominator
- Case definition: Laboratory methods and clinical case definitions

- Incidence or prevalence of VZV
- Mortality and hospitalization rates associated with the VZV
- Characteristics of VZV cases: age, gender, HIV status, access to Acyclovir or other antiviral treatment, vaccination status

Risk of bias assessment for included studies

We will adapt the risk of bias and quality assessment tool developed by Hoy *et al* and modified by others for evaluating prevalence studies (14,15). This scoring tool, which will be used on all the included studies, examines the internal and external validity by taking into account study design, methodology and the presence of bias. This risk of bias and quality assessment tool is given in Table 2.

This review will not include unpublished reports. Furthermore, if data is collected from health systems, it is automatically limited to medically attended cases and may miss milder cases or persons who have less access to healthcare services, which occurs commonly in Africa. We, therefore, acknowledge that our study is likely to underestimate the burden of the VZV-associated disease in Africa.

Data synthesis

The results from the included studies will be reported as incidence and/or prevalence of varicella or herpes zoster, as well as hospitalization and death rates. A trend analysis will be done to investigate the trend of varicella or herpes zoster burden in Africa over time. R-programming software will be used to perform the statistical calculations.

If the studies included have a high heterogeneity (this will be examined by chi-squared test of homogeneity and quantified using the I-squared statistic) the findings will be presented in a narrative form.

Subgroup analysis

The findings from each country will be reported separately as part of a subgroup analysis. In addition, further subgroup analyses will be conducted, where sufficient data exist, based on whether the study was conducted in the community or in a healthcare centre, the income status of the countries as classified by the World Bank, national background HIV/AIDS prevalence rates and geographical setting or population density (urban vs rural settings) (16).

Sensitivity analysis

For the meta-analysed data, a sensitivity analysis will be performed to determine if the exclusion of highly biased studies (based on the risk of bias assessment) will change the findings of the meta-analysis.

Reporting of the review

The findings of this systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines, and will include a summary flow diagram on how articles were selected, as well as a list of excluded studies and the reasons for exclusion. Narrative reporting will be used to describe any qualitative data from the studies.

Discussion

While there is a large amount of epidemiological data on VZV in high income countries, there is limited data from African countries. As there are major differences in the epidemiology of VZV-associated diseases between high- and low- or middle-income countries (LMIC's), data from high-income countries cannot be extrapolated to LMIC's. A review from Latin America, for instance, found a much higher incidence of varicella compared to the USA, while a review from Asia found that a significant proportion of individuals are infected after childhood for the first time with varicella (3,17). Our proposed systematic review will generate useful data on the burden of VZV in Africa, taking into account the high burden of HIV/AIDS. These results could be used as the first step towards developing vaccination control plans for varicella and zoster on the continent.

If the VZV-associated disease burden in Africa is found to be high, follow-up studies would be needed to determine the cost-effectiveness and feasibility of vaccination in this setting. It has been suggested that universal infant immunization against varicella would not be possible in LMIC's, and that high risk groups, such as immunocompromised individuals or healthcare workers, should be targeted for vaccination instead (1). But here again, more epidemiological data would be needed to inform such decisions.

One of our study limitations is that only severe cases of VZV-associated cases are hospitalized or reported and in Africa, poor access to healthcare services is prevalent. Therefore, we are very likely to underestimate the burden of these diseases in our review. As such, even if our study finds the VZV-associated disease

burden is low on the continent, we suggest that this review needs to be continuously updated. In addition, access to healthcare should improve over time and more data on VZV-associated cases will become available. Updating the review is also important as the epidemiology of many diseases, including varicella and zoster, will continue to change over time, as demographic changes occur and urbanisation increases. It is also important that the background epidemiology of vaccine-preventable diseases on the continent are known and updated regularly, as part of a general surveillance programme and for the review of vaccination policies.

Authors' contributions

HSH and GDH conceived the study. HSH developed the study protocol and will implement the systematic review under the supervision of BMK. JC provided the statistical analysis plan of the study and will aid in the final data analysis. HSH and LHA will perform the study search, screening and extraction of data under the guidance of JC, RM, GDH and BMK. HSH wrote the first draft of the protocol. All authors gave input to the final draft of the protocol.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

All authors have no competing interests.

Ethics approval

No ethics approval required as this is a protocol for a systematic review, which will use already published data.

Executive licence statement

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Table 1: PubMed Search Strategy

Query number	Search terms
#1	"Herpesvirus 3, Human"[Mesh] OR “Varicella zoster”
#2	"Chickenpox"[Mesh] OR varicella OR "Herpes Zoster"[Mesh]
#3	#1 OR #2
#4	epidemiology OR prevalence OR incidence OR burden
#5	hospitalisation OR hospitalization OR mortality OR “case-fatality rate”
#6	#4 OR #5
#7	#3 AND #6
#8	"Africa"[Mesh]
#9	(Algeria) OR (Angola) OR (Benin OR Dahomey) OR (Botswana) OR (“Burkina Faso” OR “Republic of Upper Volta”) OR “Republic of Upper Volta”) OR (Burundi) OR (Cameroon) OR ("Canary Islands") OR ("Cape Verde") OR (“Central African Republic”) OR (Chad) OR (Comoros) OR (Congo) OR (“Democratic Republic Congo” OR (Zaire)) OR (Djibouti) OR (Egypt) OR ("Equatorial Guinea") OR (Eritrea) OR (Ethiopia) OR (Gabon) OR (Gambia) OR (Ghana) OR (Guinea) OR ("Guinea Bissau") OR (“Ivory Coast” OR "Cote D'ivoire") OR (Kenya) OR (Lesotho) OR (Liberia) OR ((Libya) OR (Libia) OR (Jamahiriya) OR (Jamahiryia)) OR (Madagascar) OR (Malawi) OR (Mali) OR (Mauritania) OR (Mauritius) OR (Morocco) OR ((Mozambique) OR (Mocambique)) OR ((Namibia) OR “South West Africa”) OR (Niger) OR (Nigeria) OR (Reunion) OR (Rwanda) OR ("Sao Tome") OR (Senegal) OR (Seychelles) OR ("Sierra Leone") OR (Somalia) OR ("South Africa") OR ("St Helena") OR (“South Sudan”) OR (Sudan) OR (Swaziland) OR (Tanzania) OR (Togo) OR (Tunisia) OR (Uganda) OR ("Western Sahara") OR (Zambia) OR (Zimbabwe OR Rhodesia) OR (South* AND Africa*) OR (West* AND Africa*) OR (East* AND Africa*) OR (North* AND Africa*) OR (Central* AND Africa*) OR (Sub-Saharan Africa*) OR (Subsaharan Africa*) OR (Africa*) NOT ((Guinea Pig*) OR ((Aspergillus Niger) OR "Aspergillus Niger”))
#10	#8 OR #9
#11	#7 AND #10

Table 2: Risk of bias and quality assessment for prevalence studies (14)

Items	Quality score
External validity	
1. Was the study's target population a close representation of the national population in relations to relevant variables	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of non-response bias minimal?	(1 point)
Total	(4 points)
Internal validity	
1. Were data collected directly from the participants (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all participants?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
Total	(6 points)

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Abstract

Introduction

Varicella zoster virus (VZV) causes varicella (chicken pox) and herpes zoster (shingles). Worldwide, these diseases are associated with significant morbidity. Most of the epidemiological data on VZV come from high-income countries. There are little data on VZV in Africa, where tropical climates and high HIV/AIDS prevalence rates are expected to impact the epidemiology of VZV.

Safe and effective vaccinations for both varicella and herpes zoster exist, but are not routinely used in Africa. There are very little data available on VZV disease burden in Africa that could guide the introduction of these vaccines on the continent. Our aim is to conduct a systematic review of the VZV-associated morbidity and mortality in Africa, which will provide critical information that could be used to develop vaccination policies against these diseases in Africa.

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Strengths and limitations of this study

This is the first time data on VZV in Africa have been collated in a systematic review. The data will be reported according to PRISMA guidelines. The weaknesses of the study are that it only includes published studies, and therefore is at a risk of publication bias. Data from national health departments will also not be used, as there is no standardised data collection for VZV across the continent. Also if the majority of the data are collected from health care facilities, cases that do not have access to health facilities will be missed, making the study further underestimate the burden of VZV in Africa.

Background

Varicella Zoster Virus (VZV), belonging to the Herpesviridae family, causes varicella (chicken pox) and later, through endogenous reactivation, herpes zoster (shingles). Both diseases occur worldwide, and while their mortality is generally low, these diseases have a high morbidity and place a large burden on healthcare systems and society (1). There is no synthesized literature on the burden of varicella and herpes zoster in Africa.

Varicella is characterised by a vesicular rash and fever, and in children is usually a mild, self-limiting illness. Complications, however, do occur, particularly in infants, pregnant women, adults and immunocompromised individuals, including those with HIV (1,2). Globally, there are 4.2 million cases of severe varicella that result in hospitalization or death each year (2). Prior to widespread usage of vaccines against varicella in temperate high income countries, 13-16 cases of varicella per 1000 population occurred annually, with mostly children aged 1-9 years affected (1). In these settings more than 90% of the population becomes infected with VZV before adolescence (2). In tropical regions, primary infection of varicella tends to occur at a later stage, resulting in a larger population of susceptible adults and potentially a higher proportion of severe cases (2,3).

After an episode of varicella, VZV remains dormant in the dorsal root ganglia, and reactivation results in zoster, a painful vesicular rash, usually confined to one dermatome (4). The incidence of herpes zoster increases with increasing age, especially after 50 years of life. For example, half of all 85 year old individuals have experienced an episode of herpes zoster (2). Decreasing cell mediated immunity due

to, for example, HIV infection, cancer, diabetes mellitus and immunosuppressive treatment also increase the risk of zoster (2). Compared to HIV negative individuals, persons with HIV have 12-17 fold greater risk of developing zoster. In areas with a high HIV prevalence, zoster has an 85-95% positive predictive value for underlying HIV infection (5). The most common complications of zoster are post-herpetic neuralgia and ocular complications (6). About 3% of zoster patients are hospitalized (7). There are little data on zoster mortality, but studies from Europe and North America suggest that it is around 0.25 per 1 million population, mostly in the elderly (7). Timely vaccination against zoster may prevent such deaths.

Effective vaccines exist for both varicella and zoster, and are used widely in high income countries, with considerable benefits (2). In 1998, WHO recommended the introduction of routine childhood vaccination against VZV in settings where the disease has significant negative socio-economic impact (8). But vaccines against VZV are rarely used on the African continent. Introducing these vaccines would be in agreement with the Global Immunization Vision and Strategy (GIVS) of the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF). The GIVS aims to widely introduce a range of newly available vaccines and immunize more people against as many vaccine-preventable diseases as possible (9). Achieving this aim would not only promote health, but also improve equitable access to immunization (9).

Decisions to introduce vaccines against varicella and zoster in most African countries need to be guided by evidence-based data on the epidemiology and socio-economic impacts of the diseases. To the best of our knowledge, at present, there

are no synthesized VZV-associated epidemiological data in Africa. Furthermore, cost-effectiveness studies of introducing the vaccines against varicella and shingles are lacking in Africa.

The African continent has several risk factors that could result in an increased burden of VZV disease. Firstly for varicella, there is a high prevalence of HIV/AIDS and, in tropical countries, primary infections occur at an older age, both of which increase the chance of developing severe varicella. Secondly for zoster, there is an increasing ageing population, high HIV/AIDS burden and diabetes prevalence is growing (10,11). Thirdly, for both varicella and zoster, weak and overstretched healthcare systems in Africa cannot efficiently manage complications of these diseases.

Rationale

Globally, major variations in the epidemiology of VZV-associated disease exist. As such, some countries have adopted universal childhood vaccination against VZV while others recommend targeted vaccination of high risk populations only (1). In Africa, there is no collated evidence on the burden of varicella and zoster that could be used to inform decisions around vaccine introduction for these diseases. Furthermore, the impact of the HIV/AIDS pandemic on the epidemiology of VZV is also not clear, and any decisions around introduction of new vaccines on the continent would have to take this into account too.

Methods

Objective

To describe the epidemiology of VZV in Africa, taking into account both clinical diseases of varicella and zoster.

Primary objectives

- To summarize the available data on the varicella-associated morbidity and mortality in Africa
- To summarize the available data on the herpes zoster-associated morbidity and mortality in Africa

Secondary objective

To assess the impact of HIV/AIDS on the epidemiology of varicella and herpes zoster in Africa.

Eligibility criteria

Types of participants

Studies on the epidemiology of VZV, in adults and children, from any country in Africa, will be included in the review.

Case definition

Included studies must have clearly stated the case definition for varicella. The case definition for varicella, as defined by the Centres for Disease Control and Prevention (CDC), will be used for morbidity and mortality estimation (12):

Clinical description - An acute illness with diffuse maculo-papulovesicular rash, without other apparent cause.

Laboratory criteria - Isolation of varicella virus from a clinical specimen, OR Varicella antigen detected by direct fluorescent antibody test, OR Varicella-specific nucleic acid detected by polymerase chain reaction (PCR), OR Significant rise in serum anti-varicella immunoglobulin G (IgG) antibody level by any standard serologic assay.

The case definition of herpes zoster uses only the clinical description (painful maculo-papulovesicular rash, usually confined to a dermatome), as it has been shown to be distinctive enough to make an accurate clinical diagnosis (13).

Inclusion criteria

Studies will be included if they are conducted in Africa, measure or report any of the primary outcomes listed below and have a case definition for varicella or herpes zoster.

Exclusion criteria

Studies will be excluded from this review if they are not conducted in Africa, do not measure any of the primary outcomes listed below and have not stated a case definition of varicella or herpes zoster.

Outcomes

Primary outcomes

- Incidence or prevalence of varicella or herpes zoster

- Hospitalization rates associated with varicella or herpes zoster

- Total deaths associated with varicella or herpes zoster

Secondary outcomes

- Proportion of varicella or herpes zoster hospitalizations and/or deaths associated with HIV/AIDS

Type of studies

Case-series, cross-sectional, cohort and intervention studies will be included. All studies published from January 1974 to September 2015, will be included without language restrictions. Google translator software will first be used to enable preliminary screening of non-English records by titles or abstracts that appear likely to be included. If the article still appears likely for inclusion, then we will seek translation support from our network of collaborators who is a native speaker of the language used in the article. If unsuccessful with this option, then we will seek professional translation services.

Search strategy

The literature search strategy will use both text words and medical subject heading (MeSH) terms and will include the following: varicella zoster virus, human herpes virus 3, varicella, chicken pox, herpes zoster or shingles, as well as prevalence, incidence, epidemiology, burden, hospitalisation or hospitalization, mortality or case-fatality rates. These terms will be adapted for each database and then be combined with a relevant filter to select out studies from the African continent only. An example of the PubMed search strategy is shown in Table 1.

Electronic databases

The following electronic databases will be searched: PubMed, Scopus, Africa-wide, Embase, WHOLIS, PDQ-Evidence, CENTRAL, CINAHL and Web of Science.

Selection of eligible studies

The first and the second authors (HSH and LHA) will screen the search outputs using titles and abstracts. In addition, study setting, study design, methods as well as study outcomes will be evaluated. The two authors will then independently read through the full text of all potentially eligible studies to assess if inclusion criteria are met. Discrepancies in the list of included studies between the two authors will be resolved through discussion and consensus, with the assistance of the last author (BMK).

Data collection process

Data will be extracted from the included studies and recorded on a pre-designed form. If need be, corresponding authors for the included studies will be contacted where the data are unclear. The following data will be extracted from the included studies:

- Study characteristics: year of the study publication, study design and objectives of the study
- Study population: country, community or healthcare facility based, and the source of the denominator
- Case definition: Laboratory methods and clinical case definitions
- Incidence or prevalence of VZV
- Mortality and hospitalization rates associated with the VZV
- Prevalence of complications of VZV not requiring hospitalization, e.g. post-herpetic neuralgia
- Characteristics of VZV cases: age, gender, HIV status, access to Acyclovir or other antiviral treatment, vaccination status

Risk of bias assessment and strength of the cumulative results for included studies

We will adapt the risk of bias and quality assessment tool developed by Hoy *et al* and modified by others for evaluating prevalence studies (14,15). This scoring tool, which will be used on all the included studies, examines the internal and external validity by taking into account study design, methodology and the presence of bias. Two authors (HSH and LHA) will independently score the risk of bias using the tool and a *Kappa* agreement will be calculated. This risk of bias and quality assessment tool is given in Table 2. The strength of the cumulative evidence will be based on the average score obtained following the criteria described in Table 2. An average score of 1, 2, 3 and 4 points would imply the cumulative evidence is weak, average, strong and very strong respectively.

This review will not include unpublished reports, and therefore is at a risk of publication bias. As there is no standardised data collection for VZV across the continent, data from national health departments will also not be used. The practical difficulties of collecting this data are a further reason for not collecting it and this is a limitation of our study. Furthermore, if data are collected from health systems, it is automatically limited to medically attended cases and may miss milder cases or persons who have less access to healthcare services, which occurs commonly in Africa. We, therefore, acknowledge that our study is likely to underestimate the burden of the VZV-associated disease in Africa.

Data synthesis

The results from the included studies will be reported as incidence and/or prevalence of varicella or herpes zoster, as well as hospitalization and death rates using mean

and standard deviations. A trend analysis will be done to investigate the trend of varicella or herpes zoster burden in Africa over time. R-programming software will be used to perform the statistical calculations.

If the studies included have a high heterogeneity (this will be examined by chi-squared test of homogeneity and quantified using the I-squared statistic) the findings will be presented in a narrative form that describes regions or countries with similar epidemiology of the disease.

Subgroup analysis

The findings from each country will be reported separately as part of a subgroup analysis. In addition, further subgroup analyses will be conducted, where sufficient data exist, based on whether the study was conducted in the community or in a healthcare centre, the income status of the countries as classified by the World Bank, national background HIV/AIDS prevalence rates, case definition criteria and geographical setting or population density (urban vs rural settings) (16).

Sensitivity analysis

For the meta-analysed data, a sensitivity analysis will be performed to determine if the exclusion of highly biased studies (based on the risk of bias assessment) will change the findings of the meta-analysis.

Data management

Data management will be the responsibility of the first author (HSH) in consultation with the last author (BMK). An electronic parent folder with the name of this study will be created. Subsequently, subfolders will be created that contain details of different

tasks completed such as all records retrieved, records included and excluded, risk of bias assessment results, analyses and full systematic review manuscript drafts. Two back-ups of the parent folder will be created and stored in a memory stick and a different computer.

Reporting of the review

The findings of this systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines, and will include a summary flow diagram on how articles were selected, as well as a list of excluded studies and the reasons for exclusion. Narrative reporting will be used to describe any qualitative data from the studies.

Discussion

While there is a relatively large amount of epidemiological data on VZV in high income countries, there are only limited data from African countries. As there are major differences in the epidemiology of VZV-associated diseases between high- and low- or middle-income countries (LMIC's), data from high-income countries cannot be extrapolated to LMIC's. A review from Latin America, for instance, found a much higher incidence of varicella compared to the USA, while a review from Asia found that a significant proportion of individuals are infected after childhood for the first time with varicella (3,17). Our proposed systematic review will generate useful data on the burden of VZV in Africa, taking into account the high burden of HIV/AIDS. These results could be used as the first step towards developing vaccination control plans for varicella and zoster on the continent.

If the VZV-associated disease burden in Africa is found to be high, follow-up studies would be needed to determine the cost-effectiveness and feasibility of vaccination in this setting. It has been suggested that universal infant immunization against varicella would not be possible in LMIC's, and that high risk groups, such as immunocompromised individuals or healthcare workers, should be targeted for vaccination instead (1). But here again, more epidemiological data would be needed to inform such decisions. Furthermore if the rates of VZV complications and/or hospitilization were found to be high, it would provide a strong evidence for wider accessibility of drugs like Acyclovir or those needed to treat post-herpetic neuralgia on the continent.

One of our study limitations is that only severe cases of VZV-associated cases are hospitalized or reported and in Africa, poor access to healthcare services is prevalent. Therefore, we are very likely to underestimate the burden of these diseases in our review. As such, even if our study finds the VZV-associated disease burden is low on the continent, we suggest that this review needs to be continuously updated. In addition, access to healthcare should improve over time and more data on VZV-associated cases will become available. Updating the review is also important as the epidemiology of many diseases, including varicella and zoster, will continue to change over time, as demographic changes occur and urbanisation increases. It is also important that the background epidemiology of vaccine-preventable diseases on the continent are known and updated regularly, as part of a general surveillance programme and for the review of vaccination policies.

Authors' contributions

HSH and GDH conceived the study. HSH developed the study protocol and will implement the systematic review under the supervision of BMK. JC provided the statistical analysis plan of the study and will aid in the final data analysis. HSH and LHA will perform the study search, screening and extraction of data under the guidance of JC, RM, GDH and BMK. HSH wrote the first draft of the protocol. All authors gave input to the final draft of the protocol.

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fund the costs associated with the dissemination of the results, including publications.

Competing interests

All authors have no competing interests.

Ethics approval

No ethics approval required as this is a protocol for a systematic review, which will use already published data.

Executive licence statement

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Table 1: PubMed Search Strategy

Query number	Search terms
#1	"Herpesvirus 3, Human"[Mesh] OR “Varicella zoster”
#2	"Chickenpox"[Mesh] OR varicella OR "Herpes Zoster"[Mesh]
#3	#1 OR #2
#4	epidemiology OR prevalence OR incidence OR burden
#5	hospitalisation OR hospitalization OR mortality OR “case-fatality rate”
#6	#4 OR #5
#7	#3 AND #6
#8	"Africa"[Mesh]
#9	(Algeria) OR (Angola) OR (Benin OR Dahomey) OR (Botswana) OR (“Burkina Faso” OR “Republic of Upper Volta”) OR (Burundi) OR (Cameroon) OR ("Canary Islands") OR ("Cape Verde") OR (“Central African Republic”) OR (Chad) OR (Comoros) OR (Congo) OR (“Democratic Republic of Congo” OR (Zaire)) OR (Djibouti) OR (Egypt) OR ("Equatorial Guinea") OR (Eritrea) OR (Ethiopia) OR (Gabon) OR (Gambia) OR (Ghana) OR (Guinea) OR ("Guinea Bissau") OR (“Ivory Coast” OR "Cote D'ivoire") OR (Kenya) OR (Lesotho) OR (Liberia) OR ((Libya) OR (Libia) OR (Jamahiriya) OR (Jamahiryia)) OR (Madagascar) OR (Malawi) OR (Mali) OR (Mauritania) OR (Mauritius) OR (Morocco) OR ((Mozambique) OR (Mocambique)) OR ((Namibia) OR “South West Africa”) OR (Niger) OR (Nigeria) OR (Reunion) OR (Rwanda) OR ("Sao Tome") OR (Senegal) OR (Seychelles) OR ("Sierra Leone") OR (Somalia) OR ("South Africa") OR ("St Helena") OR (“South Sudan”) OR (Sudan) OR (Swaziland) OR (Tanzania) OR (Togo) OR (Tunisia) OR (Uganda) OR ("Western Sahara") OR (Zambia) OR (Zimbabwe OR Rhodesia) OR (South* AND Africa*) OR (West* AND Africa*) OR (East* AND Africa*) OR (North* AND Africa*) OR (Central* AND Africa*) OR (Sub-Saharan Africa*) OR (Subsaharan Africa*) OR (Africa*) NOT ((Guinea Pig*) OR ((Aspergillus Niger) OR "Aspergillus Niger”))
#10	#8 OR #9
#11	#7 AND #10

Table 2: Risk of bias and quality assessment for prevalence studies (14)

Items	Quality score
External validity	
1. Was the study's target population a close representation of the national population in relations to relevant variables	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of non-response bias minimal?	(1 point)
Total	(4 points)
Internal validity	
1. Were data collected directly from the participants (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all participants?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
Total	(6 points)

Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol

PRISMA-P Checklist

		Item no.		Included	Page no.
Administrative Information					
Title	Identification	1a		Yes	1
	Update	1b	This is a new protocol, not an update of a previous review	No	N/A
Registration		2	PROSPERO: CRD42015026144	Yes	3
Authors	Contact	3a		Yes	1
	Contributions	3b		Yes	14
Amendments		4	This is not an amendment to a previously published protocol	No	N/A
Support	Sources	5a	Vaccines For Africa Initiative (VACFA) will assist with costs for the dissemination of results including publications	Yes	14, 15
	Sponsor	5b	There is no sponsor	No	N/A
	Role of sponsor or funder	5c	There is no sponsor	No	N/A
Introduction					
Rationale		6		Yes	6
Objectives		7		Yes	7
Methods					
Eligibility		8		Yes	7,8
Information sources		9		Yes	8, 9
Search strategy		10		Yes	9, 18
Study records	Data management	11a		Yes	12
	Selection process	11b		Yes	9, 10
	Data collection process	11c		Yes	10
	Data items	12	This is a prevalence systematic review and therefore, does not have all PICO variables. Variables for which data will be sought are listed and defined	Yes	10
Outcomes and prioritization		13		Yes	8, 9

Risk of bias in individual studies		14		Yes	12
Data synthesis		15a			11
		15b		Yes	11,12
		15c	Sensitivity and subgroup analyses	Yes	12
		15d		Yes	12
Meta-bias(es)		16		Yes	12
Confidence in cumulative evidence		17		Yes	11

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Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol

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Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol

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Abstract

Introduction

Varicella zoster virus (VZV) causes varicella (chicken pox) and herpes zoster (shingles). Worldwide, these diseases are associated with significant morbidity. Most of the epidemiological data on VZV come from high-income countries. There are little data on VZV in Africa, where tropical climates and high HIV/AIDS prevalence rates are expected to impact the epidemiology of VZV.

Safe and effective vaccinations for both varicella and herpes zoster exist, but are not routinely used in Africa. There are very little data available on VZV disease burden in Africa that could guide the introduction of these vaccines on the continent. Our aim is to conduct a systematic review of the VZV-associated morbidity and mortality in Africa, which will provide critical information that could be used to develop vaccination policies against these diseases in Africa.

Methods and Analysis

Electronic databases will be searched and all studies published after 1974 that meet predefined criteria will be assessed. The primary outcomes for the study are VZV incidence/prevalence, hospitalization rates and total death rates. The secondary outcome for this study is the proportion of VZV hospitalizations and/or deaths associated with HIV/AIDS.

Two reviewers will screen the titles and abstracts, and then independently review the full texts to determine if studies are eligible for inclusion. A risk of bias and quality assessment tool will be used to score all included studies. Following standardised data extraction, a trend analysis using R-programming software will be done to

investigate the trend of VZV. Depending on the characteristics of included studies, sub-group analyses will be performed. This review will be reported according to the PRISMA guidelines.

Ethics and Dissemination

As this is a protocol for a systematic review, which will use already published data, no ethics approval is required. Findings will be disseminated in peer-reviewed journals.

Systematic review registration: PROSPERO CRD42015026144 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026144)

Strengths and limitations of this study

This is the first time data on VZV in Africa have been collated in a systematic review. The data will be reported according to PRISMA guidelines. The weaknesses of the study are that it only includes published studies, and therefore is at a risk of publication bias. Data from national health departments will also not be used, as there is no standardised data collection for VZV across the continent. Also if the majority of the data are collected from health care facilities, cases that do not have access to health facilities will be missed, making the study further underestimate the burden of VZV in Africa.

Background

Varicella Zoster Virus (VZV), belonging to the Herpesviridae family, causes varicella (chicken pox) and later, through endogenous reactivation, herpes zoster (shingles). Both diseases occur worldwide, and while their mortality is generally low, these diseases have a high morbidity and place a large burden on healthcare systems and society (1). There is no synthesized literature on the burden of varicella and herpes zoster in Africa.

Varicella is characterised by a vesicular rash and fever, and in children is usually a mild, self-limiting illness. Complications, however, do occur, particularly in infants, pregnant women, adults and immunocompromised individuals, including those with HIV (1,2). Globally, there are 4.2 million cases of severe varicella that result in hospitalization or death each year (2). Prior to widespread usage of vaccines against varicella in temperate high income countries, 13-16 cases of varicella per 1000 population occurred annually, with mostly children aged 1-9 years affected (1). In these settings more than 90% of the population becomes infected with VZV before adolescence (2). In tropical regions, primary infection of varicella tends to occur at a later stage, resulting in a larger population of susceptible adults and potentially a higher proportion of severe cases (2,3).

After an episode of varicella, VZV remains dormant in the dorsal root ganglia, and reactivation results in zoster, a painful vesicular rash, usually confined to one dermatome (4). The incidence of herpes zoster increases with increasing age, especially after 50 years of life. For example, half of all 85 year old individuals have experienced an episode of herpes zoster (2). Decreasing cell mediated immunity due

to, for example, HIV infection, cancer, diabetes mellitus and immunosuppressive treatment also increase the risk of zoster (2). Compared to HIV negative individuals, persons with HIV have 12-17 fold greater risk of developing zoster. In areas with a high HIV prevalence, zoster has an 85-95% positive predictive value for underlying HIV infection (5). The most common complications of zoster are post-herpetic neuralgia and ocular complications (6). About 3% of zoster patients are hospitalized (7). There are little data on zoster mortality, but studies from Europe and North America suggest that it is around 0.25 per 1 million population, mostly in the elderly (7). Timely vaccination against zoster may prevent such deaths.

Effective vaccines exist for both varicella and zoster, and are used widely in high income countries, with considerable benefits (2). In 1998, WHO recommended the introduction of routine childhood vaccination against VZV in settings where the disease has significant negative socio-economic impact (8). But vaccines against VZV are rarely used on the African continent. Introducing these vaccines would be in agreement with the Global Immunization Vision and Strategy (GIVS) of the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF). The GIVS aims to widely introduce a range of newly available vaccines and immunize more people against as many vaccine-preventable diseases as possible (9). Achieving this aim would not only promote health, but also improve equitable access to immunization (9).

Decisions to introduce vaccines against varicella and zoster in most African countries need to be guided by evidence-based data on the epidemiology and socio-economic impacts of the diseases. To the best of our knowledge, at present, there

are no synthesized VZV-associated epidemiological data in Africa. Furthermore, cost-effectiveness studies of introducing the vaccines against varicella and shingles are lacking in Africa.

The African continent has several risk factors that could result in an increased burden of VZV disease. Firstly for varicella, there is a high prevalence of HIV/AIDS and, in tropical countries, primary infections occur at an older age, both of which increase the chance of developing severe varicella. Secondly for zoster, there is an increasing ageing population, high HIV/AIDS burden and diabetes prevalence is growing (10,11). Thirdly, for both varicella and zoster, weak and overstretched healthcare systems in Africa cannot efficiently manage complications of these diseases.

Rationale

Globally, major variations in the epidemiology of VZV-associated disease exist. As such, some countries have adopted universal childhood vaccination against VZV while others recommend targeted vaccination of high risk populations only (1). In Africa, there is no collated evidence on the burden of varicella and zoster that could be used to inform decisions around vaccine introduction for these diseases. Furthermore, the impact of the HIV/AIDS pandemic on the epidemiology of VZV is also not clear, and any decisions around introduction of new vaccines on the continent would have to take this into account too.

Methods

Objective

To describe the epidemiology of VZV in Africa, taking into account both clinical diseases of varicella and zoster.

Primary objectives

- To summarize the available data on the varicella-associated morbidity and mortality in Africa
- To summarize the available data on the herpes zoster-associated morbidity and mortality in Africa

Secondary objective

To assess the impact of HIV/AIDS on the epidemiology of varicella and herpes zoster in Africa.

Eligibility criteria

Types of participants

Studies on the epidemiology of VZV, in adults and children, from any country in Africa, will be included in the review.

Case definition

Included studies must have clearly stated the case definition for varicella. The case definition for varicella, as defined by the Centres for Disease Control and Prevention (CDC), will be used for morbidity and mortality estimation (12):

Clinical description - An acute illness with diffuse maculo-papulovesicular rash, without other apparent cause.

Laboratory criteria - Isolation of varicella virus from a clinical specimen, OR Varicella antigen detected by direct fluorescent antibody test, OR Varicella-specific nucleic acid detected by polymerase chain reaction (PCR), OR Significant rise in serum anti-varicella immunoglobulin G (IgG) antibody level by any standard serologic assay.

The case definition of herpes zoster uses only the clinical description (painful maculo-papulovesicular rash, usually confined to a dermatome), as it has been shown to be distinctive enough to make an accurate clinical diagnosis (13).

Inclusion criteria

Studies will be included if they are conducted in Africa, measure or report any of the primary outcomes listed below and have a case definition for varicella or herpes zoster.

Exclusion criteria

Studies will be excluded from this review if they are not conducted in Africa, do not measure any of the primary outcomes listed below and have not stated a case definition of varicella or herpes zoster.

Outcomes

Primary outcomes

- Incidence or prevalence of varicella or herpes zoster

- Hospitalization rates associated with varicella or herpes zoster

- Total deaths associated with varicella or herpes zoster

Secondary outcomes

- Proportion of varicella or herpes zoster hospitalizations and/or deaths associated with HIV/AIDS

Type of studies

Case-series, cross-sectional, cohort and intervention studies will be included. All studies published from January 1974 to September 2015, will be included without language restrictions. Google translator software will first be used to enable preliminary screening of non-English records by titles or abstracts that appear likely to be included. If the article still appears likely for inclusion, then we will seek translation support from our network of collaborators who is a native speaker of the language used in the article. If unsuccessful with this option, then we will seek professional translation services.

Search strategy

The literature search strategy will use both text words and medical subject heading (MeSH) terms and will include the following: varicella zoster virus, human herpes virus 3, varicella, chicken pox, herpes zoster or shingles, as well as prevalence, incidence, epidemiology, burden, hospitalisation or hospitalization, mortality or case-fatality rates. These terms will be adapted for each database and then be combined with a relevant filter to select out studies from the African continent only. An example of the PubMed search strategy is shown in Table 1.

Electronic databases

The following electronic databases will be searched: PubMed, Scopus, Africa-wide, Embase, WHOLIS, PDQ-Evidence, CENTRAL, CINAHL and Web of Science.

Selection of eligible studies

The first and the second authors (HSH and LHA) will screen the search outputs using titles and abstracts. In addition, study setting, study design, methods as well as study outcomes will be evaluated. The two authors will then independently read through the full text of all potentially eligible studies to assess if inclusion criteria are met. Discrepancies in the list of included studies between the two authors will be resolved through discussion and consensus, with the assistance of the last author (BMK).

Data collection process

Data will be independently extracted from the included studies by two reviewers, and recorded on a pre-designed form. If need be, corresponding authors for the included studies will be contacted where the data are unclear. The following data will be extracted from the included studies:

- Study characteristics: year of the study publication, study design and objectives of the study
- Study population: country, community or healthcare facility based, and the source of the denominator
- Case definition: Laboratory methods and clinical case definitions
- Incidence or prevalence of VZV
- Mortality and hospitalization rates associated with the VZV
- Prevalence of complications of VZV not requiring hospitalization, e.g. post-herpetic neuralgia
- Characteristics of VZV cases: age, gender, HIV status, access to Acyclovir or other antiviral treatment, vaccination status

Risk of bias assessment and strength of the cumulative results for included studies

We will adapt the risk of bias and quality assessment tool developed by Hoy *et al* and modified by others for evaluating prevalence studies (14,15). This scoring tool, which will be used on all the included studies, examines the internal and external validity by taking into account study design, methodology and the presence of bias. Two authors (HSH and LHA) will independently score the risk of bias using the tool and a *Kappa* agreement will be calculated. This risk of bias and quality assessment tool is given in Table 2. The strength of the cumulative evidence will be based on the average score obtained following the criteria described in Table 2. An average score of 1, 2, 3 and 4 points would imply the cumulative evidence is weak, average, strong and very strong respectively.

This review will not include unpublished reports, and therefore is at a risk of publication bias. As there is no standardised data collection for VZV across the continent, data from national health departments will also not be used. The practical difficulties of collecting this data are a further reason for not collecting it and this is a limitation of our study. Furthermore, if data are collected from health systems, it is automatically limited to medically attended cases and may miss milder cases or persons who have less access to healthcare services, which occurs commonly in Africa. We, therefore, acknowledge that our study is likely to underestimate the burden of the VZV-associated disease in Africa.

Data synthesis

The results from the included studies will be reported as incidence and/or prevalence of varicella or herpes zoster, as well as hospitalization and death rates using mean

and standard deviations. A trend analysis will be done to investigate the trend of varicella or herpes zoster burden in Africa over time. R-programming software will be used to perform the statistical calculations.

If the studies included have a high heterogeneity (this will be examined by chi-squared test of homogeneity and quantified using the I-squared statistic) the findings will be presented in a narrative form that describes regions or countries with similar epidemiology of the disease.

Subgroup analysis

The findings from each country will be reported separately as part of a subgroup analysis. In addition, further subgroup analyses will be conducted, where sufficient data exist, based on whether the study was conducted in the community or in a healthcare centre, the income status of the countries as classified by the World Bank, national background HIV/AIDS prevalence rates, case definition criteria and geographical setting or population density (urban vs rural settings) (16).

Sensitivity analysis

For the meta-analysed data, a sensitivity analysis will be performed to determine if the exclusion of highly biased studies (based on the risk of bias assessment) will change the findings of the meta-analysis.

Data management

Data management will be the responsibility of the first author (HSH) in consultation with the last author (BMK). An electronic parent folder with the name of this study will be created. Subsequently, subfolders will be created that contain details of different

tasks completed such as all records retrieved, records included and excluded, risk of bias assessment results, analyses and full systematic review manuscript drafts. Two back-ups of the parent folder will be created and stored in a memory stick and a different computer.

Reporting of the review

The findings of this systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines, and will include a summary flow diagram on how articles were selected, as well as a list of excluded studies and the reasons for exclusion. Narrative reporting will be used to describe any qualitative data from the studies.

Discussion

While there is a relatively large amount of epidemiological data on VZV in high income countries, there are only limited data from African countries. As there are major differences in the epidemiology of VZV-associated diseases between high- and low- or middle-income countries (LMIC's), data from high-income countries cannot be extrapolated to LMIC's. A review from Latin America, for instance, found a much higher incidence of varicella compared to the USA, while a review from Asia found that a significant proportion of individuals are infected after childhood for the first time with varicella (3,17). Our proposed systematic review will generate useful data on the burden of VZV in Africa, taking into account the high burden of HIV/AIDS. These results could be used as the first step towards developing vaccination control plans for varicella and zoster on the continent.

If the VZV-associated disease burden in Africa is found to be high, follow-up studies would be needed to determine the cost-effectiveness and feasibility of vaccination in this setting. It has been suggested that universal infant immunization against varicella would not be possible in LMIC's, and that high risk groups, such as immunocompromised individuals or healthcare workers, should be targeted for vaccination instead (1). But here again, more epidemiological data would be needed to inform such decisions. Furthermore if the rates of VZV complications and/or hospitilization were found to be high, it would provide a strong evidence for wider accessibility of drugs like Acyclovir or those needed to treat post-herpetic neuralgia on the continent.

One of our study limitations is that only severe cases of VZV-associated cases are hospitalized or reported and in Africa, poor access to healthcare services is prevalent. Therefore, we are very likely to underestimate the burden of these diseases in our review. As such, even if our study finds the VZV-associated disease burden is low on the continent, we suggest that this review needs to be continuously updated. In addition, access to healthcare should improve over time and more data on VZV-associated cases will become available. Updating the review is also important as the epidemiology of many diseases, including varicella and zoster, will continue to change over time, as demographic changes occur and urbanisation increases. It is also important that the background epidemiology of vaccine-preventable diseases on the continent are known and updated regularly, as part of a general surveillance programme and for the review of vaccination policies.

Authors' contributions

HSH and GDH conceived the study. HSH developed the study protocol and will implement the systematic review under the supervision of BMK. JC provided the statistical analysis plan of the study and will aid in the final data analysis. HSH and LHA will perform the study search, screening and extraction of data under the guidance of JC, RM, GDH and BMK. HSH wrote the first draft of the protocol. All authors gave input to the final draft of the protocol.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The Vaccines For Africa Initiative (VACFA) will

fund the costs associated with the dissemination of the results, including publications.

Competing interests

All authors have no competing interests.

Ethics approval

No ethics approval required as this is a protocol for a systematic review, which will use already published data.

Executive licence statement

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Table 1: PubMed Search Strategy

Query number	Search terms
#1	"Herpesvirus 3, Human"[Mesh] OR “Varicella zoster”
#2	"Chickenpox"[Mesh] OR varicella OR "Herpes Zoster"[Mesh]
#3	#1 OR #2
#4	epidemiology OR prevalence OR incidence OR burden
#5	hospitalisation OR hospitalization OR mortality OR “case-fatality rate”
#6	#4 OR #5
#7	#3 AND #6
#8	"Africa"[Mesh]
#9	(Algeria) OR (Angola) OR (Benin OR Dahomey) OR (Botswana) OR (“Burkina Faso” OR “Republic of Upper Volta”) OR (Burundi) OR (Cameroon) OR ("Canary Islands") OR ("Cape Verde") OR (“Central African Republic”) OR (Chad) OR (Comoros) OR (Congo) OR (“Democratic Republic of Congo” OR (Zaire)) OR (Djibouti) OR (Egypt) OR ("Equatorial Guinea") OR (Eritrea) OR (Ethiopia) OR (Gabon) OR (Gambia) OR (Ghana) OR (Guinea) OR ("Guinea Bissau") OR (“Ivory Coast” OR "Cote D'ivoire") OR (Kenya) OR (Lesotho) OR (Liberia) OR ((Libya) OR (Libia) OR (Jamahiriya) OR (Jamahiryia)) OR (Madagascar) OR (Malawi) OR (Mali) OR (Mauritania) OR (Mauritius) OR (Morocco) OR ((Mozambique) OR (Mocambique)) OR ((Namibia) OR “South West Africa”) OR (Niger) OR (Nigeria) OR (Reunion) OR (Rwanda) OR ("Sao Tome") OR (Senegal) OR (Seychelles) OR ("Sierra Leone") OR (Somalia) OR ("South Africa") OR ("St Helena") OR (“South Sudan”) OR (Sudan) OR (Swaziland) OR (Tanzania) OR (Togo) OR (Tunisia) OR (Uganda) OR ("Western Sahara") OR (Zambia) OR (Zimbabwe OR Rhodesia) OR (South* AND Africa*) OR (West* AND Africa*) OR (East* AND Africa*) OR (North* AND Africa*) OR (Central* AND Africa*) OR (Sub-Saharan Africa*) OR (Subsaharan Africa*) OR (Africa*) NOT ((Guinea Pig*) OR ((Aspergillus Niger) OR "Aspergillus Niger”))
#10	#8 OR #9
#11	#7 AND #10

Table 2: Risk of bias and quality assessment for prevalence studies (14)

Items	Quality score
External validity	
1. Was the study's target population a close representation of the national population in relations to relevant variables	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of non-response bias minimal?	(1 point)
Total	(4 points)
Internal validity	
1. Were data collected directly from the participants (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all participants?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
Total	(6 points)

Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol

PRISMA-P Checklist

		Item no.		Included	Page no.
Administrative Information					
Title	Identification	1a		Yes	1
	Update	1b	This is a new protocol, not an update of a previous review	No	N/A
Registration		2	PROSPERO: CRD42015026144	Yes	3
Authors	Contact	3a		Yes	1
	Contributions	3b		Yes	14
Amendments		4	This is not an amendment to a previously published protocol	No	N/A
Support	Sources	5a	Vaccines For Africa Initiative (VACFA) will assist with costs for the dissemination of results including publications	Yes	14, 15
	Sponsor	5b	There is no sponsor	No	N/A
	Role of sponsor or funder	5c	There is no sponsor	No	N/A
Introduction					
Rationale		6		Yes	6
Objectives		7		Yes	7
Methods					
Eligibility		8		Yes	7,8
Information sources		9		Yes	8, 9
Search strategy		10		Yes	9, 18
Study records	Data management	11a		Yes	12
	Selection process	11b		Yes	9, 10
	Data collection process	11c		Yes	10
	Data items	12	This is a prevalence systematic review and therefore, does not have all PICO variables. Variables for which data will be sought are listed and defined	Yes	10
Outcomes and prioritization		13		Yes	8, 9

Risk of bias in individual studies		14		Yes	12
Data synthesis		15a			11
		15b		Yes	11,12
		15c	Sensitivity and subgroup analyses	Yes	12
		15d		Yes	12
Meta-bias(es)		16		Yes	12
Confidence in cumulative evidence		17		Yes	11

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Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol

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Secondary Subject Heading:	Epidemiology, Infectious diseases, Public health
Keywords:	Varicella zoster virus, chicken pox, shingles, Africa, incidence

Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol

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Abstract

Introduction

Varicella zoster virus (VZV) causes varicella (chicken pox) and herpes zoster (shingles). Worldwide, these diseases are associated with significant morbidity. Most of the epidemiological data on VZV come from high-income countries. There are little data on VZV in Africa, where tropical climates and high HIV/AIDS prevalence rates are expected to impact the epidemiology of VZV.

Safe and effective vaccinations for both varicella and herpes zoster exist, but are not routinely used in Africa. There are very little data available on VZV disease burden in Africa that could guide the introduction of these vaccines on the continent. Our aim is to conduct a systematic review of the VZV-associated morbidity and mortality in Africa, which will provide critical information that could be used to develop vaccination policies against these diseases in Africa.

Methods and Analysis

Electronic databases will be searched and all studies published after 1974 that meet predefined criteria will be assessed. The primary outcomes for the study are VZV incidence/prevalence, hospitalization rates and total death rates. The secondary outcome for this study is the proportion of VZV hospitalizations and/or deaths associated with HIV/AIDS.

Two reviewers will screen the titles and abstracts, and then independently review the full texts to determine if studies are eligible for inclusion. A risk of bias and quality assessment tool will be used to score all included studies. Following standardised data extraction, a trend analysis using R-programming software will be done to

investigate the trend of VZV. Depending on the characteristics of included studies, sub-group analyses will be performed. This review will be reported according to the PRISMA guidelines.

Ethics and Dissemination

As this is a protocol for a systematic review, which will use already published data, no ethics approval is required. Findings will be disseminated in peer-reviewed journals.

Systematic review registration: PROSPERO CRD42015026144 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026144)

Strengths and limitations of this study

This is the first time data on VZV in Africa have been collated in a systematic review. The data will be reported according to PRISMA guidelines. The weaknesses of the study are that it only includes published studies, and therefore is at a risk of publication bias. Data from national health departments will also not be used, as there is no standardised data collection for VZV across the continent. Also if the majority of the data are collected from health care facilities, cases that do not have access to health facilities will be missed, making the study further underestimate the burden of VZV in Africa.

Background

Varicella Zoster Virus (VZV), belonging to the Herpesviridae family, causes varicella (chicken pox) and later, through endogenous reactivation, herpes zoster (shingles). Both diseases occur worldwide, and while their mortality is generally low, these diseases have a high morbidity and place a large burden on healthcare systems and society (1). There is no synthesized literature on the burden of varicella and herpes zoster in Africa.

Varicella is characterised by a vesicular rash and fever, and in children is usually a mild, self-limiting illness. Complications, however, do occur, particularly in infants, pregnant women, adults and immunocompromised individuals, including those with HIV (1,2). Globally, there are 4.2 million cases of severe varicella that result in hospitalization or death each year (2). Prior to widespread usage of vaccines against varicella in temperate high income countries, 13-16 cases of varicella per 1000 population occurred annually, with mostly children aged 1-9 years affected (1). In these settings more than 90% of the population becomes infected with VZV before adolescence (2). In tropical regions, primary infection of varicella tends to occur at a later stage, resulting in a larger population of susceptible adults and potentially a higher proportion of severe cases (2,3).

After an episode of varicella, VZV remains dormant in the dorsal root ganglia, and reactivation results in zoster, a painful vesicular rash, usually confined to one dermatome (4). The incidence of herpes zoster increases with increasing age, especially after 50 years of life. For example, half of all 85 year old individuals have experienced an episode of herpes zoster (2). Decreasing cell mediated immunity due

to, for example, HIV infection, cancer, diabetes mellitus and immunosuppressive treatment also increase the risk of zoster (2). Compared to HIV negative individuals, persons with HIV have 12-17 fold greater risk of developing zoster. In areas with a high HIV prevalence, zoster has an 85-95% positive predictive value for underlying HIV infection (5). The most common complications of zoster are post-herpetic neuralgia and ocular complications (6). About 3% of zoster patients are hospitalized (7). There are little data on zoster mortality, but studies from Europe and North America suggest that it is around 0.25 per 1 million population, mostly in the elderly (7). Timely vaccination against zoster may prevent such deaths.

Effective vaccines exist for both varicella and zoster, and are used widely in high income countries, with considerable benefits (2). In 1998, WHO recommended the introduction of routine childhood vaccination against VZV in settings where the disease has significant negative socio-economic impact (8). But vaccines against VZV are rarely used on the African continent. Introducing these vaccines would be in agreement with the Global Immunization Vision and Strategy (GIVS) of the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF). The GIVS aims to widely introduce a range of newly available vaccines and immunize more people against as many vaccine-preventable diseases as possible (9). Achieving this aim would not only promote health, but also improve equitable access to immunization (9).

Decisions to introduce vaccines against varicella and zoster in most African countries need to be guided by evidence-based data on the epidemiology and socio-economic impacts of the diseases. To the best of our knowledge, at present, there

are no synthesized VZV-associated epidemiological data in Africa. Furthermore, cost-effectiveness studies of introducing the vaccines against varicella and shingles are lacking in Africa.

The African continent has several risk factors that could result in an increased burden of VZV disease. Firstly for varicella, there is a high prevalence of HIV/AIDS and, in tropical countries, primary infections occur at an older age, both of which increase the chance of developing severe varicella. Secondly for zoster, there is an increasing ageing population, high HIV/AIDS burden and diabetes prevalence is growing (10,11). Thirdly, for both varicella and zoster, weak and overstretched healthcare systems in Africa cannot efficiently manage complications of these diseases.

Rationale

Globally, major variations in the epidemiology of VZV-associated disease exist. As such, some countries have adopted universal childhood vaccination against VZV while others recommend targeted vaccination of high risk populations only (1). In Africa, there is no collated evidence on the burden of varicella and zoster that could be used to inform decisions around vaccine introduction for these diseases. Furthermore, the impact of the HIV/AIDS pandemic on the epidemiology of VZV is also not clear, and any decisions around introduction of new vaccines on the continent would have to take this into account too.

Methods

Objective

To describe the epidemiology of VZV in Africa, taking into account both clinical diseases of varicella and zoster.

Primary objectives

- To summarize the available data on the varicella-associated morbidity and mortality in Africa
- To summarize the available data on the herpes zoster-associated morbidity and mortality in Africa

Secondary objective

To assess the impact of HIV/AIDS on the epidemiology of varicella and herpes zoster in Africa.

Eligibility criteria

Types of participants

Studies on the epidemiology of VZV, in adults and children, from any country in Africa, will be included in the review.

Case definition

Included studies must have clearly stated the case definition for varicella. The case definition for varicella, as defined by the Centres for Disease Control and Prevention (CDC), will be used for morbidity and mortality estimation (12):

Clinical description - An acute illness with diffuse maculo-papulovesicular rash, without other apparent cause.

Laboratory criteria - Isolation of varicella virus from a clinical specimen, OR Varicella antigen detected by direct fluorescent antibody test, OR Varicella-specific nucleic acid detected by polymerase chain reaction (PCR), OR Significant rise in serum anti-varicella immunoglobulin G (IgG) antibody level by any standard serologic assay.

The case definition of herpes zoster uses only the clinical description (painful maculo-papulovesicular rash, usually confined to a dermatome), as it has been shown to be distinctive enough to make an accurate clinical diagnosis (13).

Inclusion criteria

Studies will be included if they are conducted in Africa, measure or report any of the primary outcomes listed below and have a case definition for varicella or herpes zoster.

Exclusion criteria

Studies will be excluded from this review if they are not conducted in Africa, do not measure any of the primary outcomes listed below and have not stated a case definition of varicella or herpes zoster.

Outcomes

Primary outcomes

- Incidence or prevalence of varicella or herpes zoster

- Hospitalization rates associated with varicella or herpes zoster

- Total deaths associated with varicella or herpes zoster

Secondary outcomes

- Proportion of varicella or herpes zoster hospitalizations and/or deaths associated with HIV/AIDS

Type of studies

Case-series, cross-sectional, cohort and intervention studies will be included. All studies published from January 1974 to September 2015, will be included without language restrictions. Google translator software will first be used to enable preliminary screening of non-English records by titles or abstracts that appear likely to be included. If the article still appears likely for inclusion, then we will seek translation support from our network of collaborators who is a native speaker of the language used in the article. If unsuccessful with this option, then we will seek professional translation services.

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The following electronic databases will be searched: PubMed, Scopus, Africa-wide, Embase, WHOLIS, PDQ-Evidence, CENTRAL, CINAHL and Web of Science.

Selection of eligible studies

The first and the second authors (HSH and LHA) will screen the search outputs using titles and abstracts. In addition, study setting, study design, methods as well as study outcomes will be evaluated. The two authors will then independently read through the full text of all potentially eligible studies to assess if inclusion criteria are met. Discrepancies in the list of included studies between the two authors will be resolved through discussion and consensus, with the assistance of the last author (BMK).

Data collection process

Data will be independently extracted from the included studies by two reviewers, and recorded on a pre-designed form. If need be, corresponding authors for the included studies will be contacted where the data are unclear. The following data will be extracted from the included studies:

- Study characteristics: year of the study publication, study design and objectives of the study
- Study population: country, community or healthcare facility based, and the source of the denominator
- Case definition: Laboratory methods and clinical case definitions
- Incidence or prevalence of VZV
- Mortality and hospitalization rates associated with the VZV
- Prevalence of complications of VZV not requiring hospitalization, e.g. post-herpetic neuralgia
- Characteristics of VZV cases: age, gender, HIV status, access to Acyclovir or other antiviral treatment, vaccination status

Risk of bias assessment and strength of the cumulative results for included studies

We will adapt the risk of bias and quality assessment tool developed by Hoy *et al* and modified by others for evaluating prevalence studies (14,15). This scoring tool, which will be used on all the included studies, examines the internal and external validity by taking into account study design, methodology and the presence of bias.

From the several quality assessment tools available, we chose to adapt the tool developed by Hoy *et al* for the following reasons: 1) it is specifically designed for prevalence studies; 2) it is an improved tool developed after a rigorous published process, including a review of the limitations of the existing tools; 3) detailed criteria to use the tool are provided, making it easier to use; 4) it has a high inter-rater agreement; and, 5) it is robust in application, and for example can be used alongside the latest tool developed by the Joanna Briggs Institute (JBI) and the Cochrane Collaboration (14, 16).

Two authors (HSH and LHA) will independently score the risk of bias using the tool and a *Kappa* agreement will be calculated. This risk of bias and quality assessment tool is given in Table 2. The strength of the cumulative evidence will be based on the average score obtained following the criteria described in Table 2. An average score of 1, 2, 3 and 4 points would imply the cumulative evidence is weak, average, strong and very strong respectively.

This review will not include unpublished reports, and therefore is at a risk of publication bias. As there is no standardised data collection for VZV across the continent, data from national health departments will also not be used. The practical difficulties of collecting this data are a further reason for not collecting it and this is a limitation of our study. Furthermore, if data are collected from health systems, it is

automatically limited to medically attended cases and may miss milder cases or persons who have less access to healthcare services, which occurs commonly in Africa. We, therefore, acknowledge that our study is likely to underestimate the burden of the VZV-associated disease in Africa.

Data synthesis

The results from the included studies will be reported as incidence and/or prevalence of varicella or herpes zoster, as well as hospitalization and death rates using mean and standard deviations. A trend analysis will be done to investigate the trend of varicella or herpes zoster burden in Africa over time. R-programming software will be used to perform the statistical calculations.

If the studies included have a high heterogeneity (this will be examined by chi-squared test of homogeneity and quantified using the I-squared statistic) the findings will be presented in a narrative form that describes regions or countries with similar epidemiology of the disease.

Subgroup analysis

The findings from each country will be reported separately as part of a subgroup analysis. In addition, further subgroup analyses will be conducted, where sufficient data exist, based on whether the study was conducted in the community or in a healthcare centre, the income status of the countries as classified by the World Bank, national background HIV/AIDS prevalence rates, case definition criteria and geographical setting or population density (urban vs rural settings) (17).

Sensitivity analysis

For the meta-analysed data, a sensitivity analysis will be performed to determine if the exclusion of highly biased studies (based on the risk of bias assessment) will change the findings of the meta-analysis.

Data management

Data management will be the responsibility of the first author (HSH) in consultation with the last author (BMK). An electronic parent folder with the name of this study will be created. Subsequently, subfolders will be created that contain details of different tasks completed such as all records retrieved, records included and excluded, risk of bias assessment results, analyses and full systematic review manuscript drafts. Two back-ups of the parent folder will be created and stored in a memory stick and a different computer.

Reporting of the review

The findings of this systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines, and will include a summary flow diagram on how articles were selected, as well as a list of excluded studies and the reasons for exclusion. Narrative reporting will be used to describe any qualitative data from the studies.

Discussion

While there is a relatively large amount of epidemiological data on VZV in high income countries, there are only limited data from African countries. As there are major differences in the epidemiology of VZV-associated diseases between high- and low- or middle-income countries (LMIC's), data from high-income countries cannot be extrapolated to LMIC's. A review from Latin America, for instance, found a much higher incidence of varicella compared to the USA, while a review from Asia found that a significant proportion of individuals are infected after childhood for the first time with varicella (3,18). Our proposed systematic review will generate useful data on the burden of VZV in Africa, taking into account the high burden of HIV/AIDS. These results could be used as the first step towards developing vaccination control plans for varicella and zoster on the continent.

If the VZV-associated disease burden in Africa is found to be high, follow-up studies would be needed to determine the cost-effectiveness and feasibility of vaccination in this setting. It has been suggested that universal infant immunization against varicella would not be possible in LMIC's, and that high risk groups, such as immunocompromised individuals or healthcare workers, should be targeted for vaccination instead (1). But here again, more epidemiological data would be needed to inform such decisions. Furthermore if the rates of VZV complications and/or hospitilization were found to be high, it would provide a strong evidence for wider accessibility of drugs like Acyclovir or those needed to treat post-herpetic neuralgia on the continent.

One of our study limitations is that only severe cases of VZV-associated cases are hospitalized or reported and in Africa, poor access to healthcare services is prevalent. Therefore, we are very likely to underestimate the burden of these diseases in our review. As such, even if our study finds the VZV-associated disease burden is low on the continent, we suggest that this review needs to be continuously updated. In addition, access to healthcare should improve over time and more data on VZV-associated cases will become available. Updating the review is also important as the epidemiology of many diseases, including varicella and zoster, will continue to change over time, as demographic changes occur and urbanisation increases. It is also important that the background epidemiology of vaccine-preventable diseases on the continent are known and updated regularly, as part of a general surveillance programme and for the review of vaccination policies.

Authors' contributions

HSH and GDH conceived the study. HSH developed the study protocol and will implement the systematic review under the supervision of BMK. JC provided the statistical analysis plan of the study and will aid in the final data analysis. HSH and LHA will perform the study search, screening and extraction of data under the guidance of JC, RM, GDH and BMK. HSH wrote the first draft of the protocol. All authors gave input to the final draft of the protocol.

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fund the costs associated with the dissemination of the results, including publications.

Competing interests

All authors have no competing interests.

Ethics approval

No ethics approval required as this is a protocol for a systematic review, which will use already published data.

Executive licence statement

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Table 1: PubMed Search Strategy

Query number	Search terms
#1	"Herpesvirus 3, Human"[Mesh] OR “Varicella zoster”
#2	"Chickenpox"[Mesh] OR varicella OR "Herpes Zoster"[Mesh]
#3	#1 OR #2
#4	epidemiology OR prevalence OR incidence OR burden
#5	hospitalisation OR hospitalization OR mortality OR “case-fatality rate”
#6	#4 OR #5
#7	#3 AND #6
#8	"Africa"[Mesh]
#9	(Algeria) OR (Angola) OR (Benin OR Dahomey) OR (Botswana) OR (“Burkina Faso” OR “Republic of Upper Volta”) OR (Burundi) OR (Cameroon) OR ("Canary Islands") OR ("Cape Verde") OR (“Central African Republic”) OR (Chad) OR (Comoros) OR (Congo) OR (“Democratic Republic of Congo” OR (Zaire)) OR (Djibouti) OR (Egypt) OR ("Equatorial Guinea") OR (Eritrea) OR (Ethiopia) OR (Gabon) OR (Gambia) OR (Ghana) OR (Guinea) OR ("Guinea Bissau") OR (“Ivory Coast” OR "Cote D'ivoire") OR (Kenya) OR (Lesotho) OR (Liberia) OR ((Libya) OR (Libia) OR (Jamahiriya) OR (Jamahiryia)) OR (Madagascar) OR (Malawi) OR (Mali) OR (Mauritania) OR (Mauritius) OR (Morocco) OR ((Mozambique) OR (Mocambique)) OR ((Namibia) OR “South West Africa”) OR (Niger) OR (Nigeria) OR (Reunion) OR (Rwanda) OR ("Sao Tome") OR (Senegal) OR (Seychelles) OR ("Sierra Leone") OR (Somalia) OR ("South Africa") OR ("St Helena") OR (“South Sudan”) OR (Sudan) OR (Swaziland) OR (Tanzania) OR (Togo) OR (Tunisia) OR (Uganda) OR ("Western Sahara") OR (Zambia) OR (Zimbabwe OR Rhodesia) OR (South* AND Africa*) OR (West* AND Africa*) OR (East* AND Africa*) OR (North* AND Africa*) OR (Central* AND Africa*) OR (Sub-Saharan Africa*) OR (Subsaharan Africa*) OR (Africa*) NOT ((Guinea Pig*) OR ((Aspergillus Niger) OR "Aspergillus Niger”))
#10	#8 OR #9
#11	#7 AND #10

Table 2: Risk of bias and quality assessment for prevalence studies (14)

Items	Quality score
External validity	
1. Was the study's target population a close representation of the national population in relations to relevant variables	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of non-response bias minimal?	(1 point)
Total	(4 points)
Internal validity	
1. Were data collected directly from the participants (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all participants?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
Total	(6 points)

Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol

PRISMA-P Checklist

		Item no.		Included	Page no.
Administrative Information					
Title	Identification	1a		Yes	1
	Update	1b	This is a new protocol, not an update of a previous review	No	N/A
Registration		2	PROSPERO: CRD42015026144	Yes	3
Authors	Contact	3a		Yes	1
	Contributions	3b		Yes	14
Amendments		4	This is not an amendment to a previously published protocol	No	N/A
Support	Sources	5a	Vaccines For Africa Initiative (VACFA) will assist with costs for the dissemination of results including publications	Yes	14, 15
	Sponsor	5b	There is no sponsor	No	N/A
	Role of sponsor or funder	5c	There is no sponsor	No	N/A
Introduction					
Rationale		6		Yes	6
Objectives		7		Yes	7
Methods					
Eligibility		8		Yes	7,8
Information sources		9		Yes	8, 9
Search strategy		10		Yes	9, 18
Study records	Data management	11a		Yes	12
	Selection process	11b		Yes	9, 10
	Data collection process	11c		Yes	10
	Data items	12	This is a prevalence systematic review and therefore, does not have all PICO variables. Variables for which data will be sought are listed and defined	Yes	10
Outcomes and prioritization		13		Yes	8, 9

Risk of bias in individual studies		14		Yes	12
Data synthesis		15a			11
		15b		Yes	11,12
		15c	Sensitivity and subgroup analyses	Yes	12
		15d		Yes	12
Meta-bias(es)		16		Yes	12
Confidence in cumulative evidence		17		Yes	11